EXHIBIT A

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ALLISON SIMPSON,	)	
	)	
	)	
Plaintiff,	)	
v.	)	**Case No.: 2:15-cv-06072-SDW-LDW**
	)	
BAYER HEALTHCARE PHARMACEUTICALS, INC., BAYER PHARMA AG, and BAYER OY,	)	
	)	
Defendants.	)	

EXPERT REPORT OF DENA R. HIXON, M.D.

Mirena Litigation
Idiopathic Intracranial Hypertension
Expert Statement of Dena R. Hixon, MD[1]

I. Background and Qualifications

A. Medical Training and Clinical Experience

I am a licensed medical doctor in the state of Maryland, with an M.D. degree from the University of Maryland School of Medicine. I completed residency training in Family Practice and received Board Certification from the American Academy of Family Practice. I also completed residency training in Obstetrics and Gynecology and received Board Certification from the American Board of Obstetrics and Gynecology. I have 13 years of clinical practice experience as an obstetrician/gynecologist.

B. FDA Regulatory Experience

For nearly 13 years (January 1999 to November 2011), I was a Medical Officer in the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). I served as a primary reviewer and team leader in the Office of New Drugs (OND), Division of Reproductive and Urologic Drug Products (DRUDP), where I reviewed and evaluated clinically relevant information regarding the safety and efficacy of women's reproductive healthcare products, including intrauterine devices (IUDs) and other contraceptives. I later became the Associate Director for Medical Affairs in the Office of Generic Drugs and evaluated a broad range of drug products used in many different clinical fields.

During my service at FDA, I was involved in reviews of Investigational New Drug (IND) applications and New Drug Applications (NDAs) for women's reproductive healthcare products, including modern intrauterine devices (IUDs) with a drug releasing component and other contraceptives. I reviewed INDs to ensure reasonable safety for studies in humans. I also reviewed protocol proposals to ensure that the proposed studies were reasonably safe and adequately designed to achieve their objectives. I reviewed NDAs for adequate evidence of safety and efficacy to meet standards for marketing approval. I also reviewed postmarketing labeling proposals, safety reports, and supplemental applications for new indications and/or for labeling changes.

In addition, I conducted and/or participated in numerous meetings with industry sponsors, including pre-IND meetings, end-of-phase 2 meetings, pre-NDA meetings, and other guidance meetings, providing advice and feedback to companies regarding study design, endpoints and/or acceptability of outcome information.

As a team leader, I trained other medical officers and evaluated their work. I also considered the reviews of all relevant disciplines and made recommendations on approval of new drug applications and various efficacy or labeling supplements, ensuring adequate evidence of safety

[1] I work as the sole member of Pharmaceutical Lifecycle Consulting, LLC, a Maryland single member limited liability company, established in December 2011.

and efficacy and maintaining consistency with policies of the division. In this role, I was responsible for the secondary review of Mirena and recommended approval of the NDA.

My work in CDER also included participating in a number of inter-office committees and working groups including the following:

1. Pregnancy Labeling Task Force, from 1999 to 2005. As a member of the task force, I contributed to the development of several guidance documents for industry and FDA reviewers, as well as the 2008 Proposed Rule on pregnancy and lactation labeling.[2]

2. FDA Drug Safety Oversight Board,[3] from its inception in 2005 until 2008. This Board was mandated by law in the FDA Amendments Act of 2007 to advise the CDER Center Director on the handling and communication of important and often emerging drug safety issues.

3. CDER Pediatric Review Committee (PeRC),[4] previously the Pediatric Implementation Team,[5] from 2002 until 2010. This committee provided consultation on and general review of pediatric information submitted to the Agency in pediatric plans and reviewed Pediatric Written Requests for studies of drug use in children.

4. CDER Pediatric Exclusivity Board, from 2002 until 2011. As a member of this board, I considered pediatric study reports submitted in response to Pediatric Written Requests to determine eligibility for extended periods of exclusivity.

I served as an instructor for CDER reviewers at internal FDA conferences, presenting the roles of the Medical Officer in the drug review process on numerous occasions. I presented clinical considerations in generic drug development to the Office of Generic Drugs and to CDER training conferences on numerous occasions. I also participated in CDER Scientific Rounds on numerous occasions as a presenter and/or panelist.

In addition, I gave presentations at public conferences, presenting the CDER review process to the CDER Forum for International Drug Regulatory Authorities, and presenting various clinical considerations in generic drug development and review at the Annual Generic Pharmaceutical Association Fall Technical Conferences.

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[2] *Proposed Rules: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, 73 Fed. Reg. 104, 30831 (May 29, 2008) (to amend 21 C.F.R. § 201).

[3] *About the Center for Drug Evaluation and Research, Drug Safety Oversight Board*, FDA.gov (updated 12/15/14).

[4] Memorandum from Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer of Food and Drugs Acting Director, Center for Drug Evaluation and Research to Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs re: Establishment of the Pediatric Review Committee (PeRC), Oct. 25, 2007, *available at* http://www fda.gov/downloads/Drugs/Development ApprovalProcess/DevelopmentResources/UCM049871.

[5] *Implementation of Pediatric Exclusivity Provisions*, hearing before the Senate Committee on Health, Education, Labor, and Pensions, May 8, 2001 (statement of Janet Woodcock), *available at* www.fda.gov.

C. Restrictions on Former Government Employees

Restrictions on former FDA Employees are set forth in Title 18, United States Code, section 207(a)(1). Former FDA employees are restricted from knowingly, with the intent to influence, representing another person or entity to the Government in connection with a particular matter—

> (A) in which the United States or the District of Columbia is a party or has a direct and substantial interest,
>
> (B) in which the person participated personally and substantially as such officer or employee, and
>
> (C) which involved a specific party or specific parties at the time of such participation,[6] or on a particular matter involving specific parties that was pending under their supervision during their last year of service.[7]

Former senior employees are also restricted from contacting their former agency with the intent to influence, on behalf of anyone seeking official action.[8]

Former government employees are not restricted from testifying about matters in which they were involved when the government is not a party in the dispute and does not have a substantial interest in the outcome.

D. Experience, Materials Reviewed, and Compensation

My current Curriculum Vitae and a list of the documents I have reviewed in preparing this statement are attached. I have reviewed documents in the IND and NDA, related FDA regulations and guidance, internal Bayer documents, and FDA communications with Bayer and its predecessors. I have also reviewed textbooks, literature reports, and publications related to the risks of unintended pregnancy, the history and use of contraception (including IUDs), and levonorgestrel products and idiopathic intracranial hypertension. I have additionally reviewed reports of plaintiffs' experts relevant to regulatory matters. Throughout this report, specific sources of information are indicated in footnotes.

I have been compensated at a rate of $600 per hour for reviewing materials and creating this report.

E. List of Cases in Which I Have Testified in the Last Four Years

In Re Topamax Litigation

Court of Common Pleas, Philadelphia County
Deposition May 1, 2013
Testimony for Defendant

[6] 18 U.S.C. § 207(a).
[7] 18 U.S.C. § 207(b).
[8] 18 U.S.C. § 207(c).

Czimmer v. Janssen Pharmaceuticals October 28-29, 2013

In The Court Of Common Pleas, First Judicial District Of Pennsylvania, Civil Trial Division, Court Testimony for Defendant

Powell v. Janssen Pharmaceuticals November 12-13, 2013

In The Court Of Common Pleas, First Judicial District Of Pennsylvania, Civil Trial Division, Court Testimony for Defendant

Anderson v. Janssen Pharmaceuticals February 25-26, 2014

In The Court Of Common Pleas, First Judicial District Of Pennsylvania, Civil Trial Division, Court Testimony for Defendant

Royal v. Novartis Pharmaceuticals Corporation June 19, 2014

Circuit Court of Cook County, Illinois
Deposition Testimony for Defendant

In Re: Mirena IUD Products Liability Litigation September 22, 2015

United States District Court, Southern District of New York
Superior Court of New Jersey Law Division, Bergen County
Deposition Testimony for Defendant

II. Brief Summary of the Issues

I understand that personal injury lawsuits have been filed against Bayer Healthcare Pharmaceuticals (Bayer),[9] the current owner of the New Drug Application (NDA) for Mirena, a levonorgestrel-releasing intrauterine system approved for long-term (5 years) contraception and for the treatment of heavy menstrual bleeding for women who choose to use the intrauterine contraceptive as their method of contraception. The plaintiffs allege that Mirena can cause idiopathic intracranial hypertension (IIH), also known as benign intracranial hypertension (BIH), or pseudotumor cerebri (PTC), and that Bayer failed to adequately alert women and their healthcare providers of this risk in the product labeling.

III. Regulatory Framework

A. Authority of the FDA in the Development and Regulation of Drugs

FDA is an agency of the United States government, situated within the Department of Health and Human Services (DHHS). It is responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices. The FDA is also responsible for the safety and security of most of

[9] Throughout this report I will use the term "Bayer" to refer to Bayer Healthcare Pharmaceuticals, as well as prior and affiliated Bayer entities as holders of the NDA.

our nation's food supply, cosmetics, dietary supplements and products that give off radiation, and for the regulation of tobacco products. Six Centers in FDA regulate products in these categories, including the Center for Drug Evaluation and Research (CDER).[10,11]

CDER is the center that ensures that safe and effective drugs are available to improve the health of people in the United States.[12] Medical devices are regulated by the Center for Devices and Radiological Health (CDRH).[13] Although both drugs and medical devices are used in the diagnosis, cure, mitigation, treatment or prevention of disease, they have different modes of action. Drugs, but not devices, work through a chemical action within or on the body or by being metabolized by the body.[14] Accordingly, the FDA premarket review and approval processes are different for drugs and devices.

The drug and medical device industries in the United States are highly regulated. FDA/CDER has authority over both drugs under development and approved drug products. It plays an important role in overseeing drug development, labeling, and advertising, and monitors the safety of drug products in order to ensure that safe and effective drugs are available to the public and that they remain safe and effective.[15]

Before FDA can grant approval for marketing of a drug product, it must determine that the data provide substantial evidence of effectiveness and reasonable safety, based on FDA's analysis of the risks vs. benefits of the drug for its intended use.[16,17] At all times FDA has ultimate authority over the product labeling, as well as continued control of quality, purity, and potency of the drug.

Under the FDCA and subsequent amendments, when new safety data show a change in the risk/benefit balance, such that the old labeling is no longer adequate for the safe and effective use of the product, FDA has authority to require labeling changes. If a company fails to submit required periodic safety reports or refuses to make labeling changes requested by FDA, the agency has authority to take enforcement action, and even remove the product from the market.[18,19] More commonly, FDA may withhold approval of any pending labeling or efficacy supplement until the company accepts FDA-requested labeling changes.

B. Regulations for Drug Development and Approval

The responsibilities of CDER in regulating drugs are largely governed by the Food, Drug and Cosmetic (FD&C) Act, as amended. FDA approval is necessary for marketing a drug in the United States. The FD&C Act was implemented in 1938 and required manufacturers to

[10] *About FDA, FDA Organization*, FDA.gov (updated 02/25/2015).
[11] *About FDA, What We Do*, FDA.gov (updated 08/05/2014).
[12] *About FDA, About the Center for Drug Evaluation and Research*, FDA.gov (updated 12/09/2014).
[13] *About FDA, About the Center for Devices and Radiologic Health*, FDA.gov (updated 01/21/2015).
[14] FD&C Act § 201(g) and (h) (21 U.S.C. §§ 321(g), (h)).
[15] *About FDA, About the Center for Drug Evaluation and Research*, FDA.gov (updated 12/09/2014).
[16] *Development & Approval Process (Drugs)*, FDA.gov (updated 10/27/2014).
[17] *How Drugs are Developed and Approved*, FDA.gov (updated 11/10/2014).
[18] *Guidance for Industry Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act*, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.
[19] *Postmarket Drug Safety Information for Patients and Providers*, FDA.gov (updated 06/15/2015).

demonstrate the safety of drug products prior to marketing approval.[20] In 1962, the Kefauver-Harris Amendment to the FD&C Act added a requirement that manufacturers also provide evidence of efficacy prior to marketing approval.[21]

The FD&C Act (and its amendments) has been codified in Title 21 of the Code of Federal Regulations (C.F.R. 21). The parts most relevant to the development and regulation of new drug products are contained within parts 200 through 369, particularly 201.57 for labeling, 312 for Investigational New Drug (IND) regulations, and 314 for New Drug Application (NDA) regulations. These parts of the C.F.R. describe the responsibilities of drug manufacturers and FDA in making safe and effective drugs available to the people of the United States.

These regulations specify what information is to be submitted in an IND and in an NDA, and describe the required format and content of labeling in detail.

C. FDA Review of an IND

Before a company can legally begin US studies of a new drug in humans, it must submit an IND,[22] including the proposed study protocols, adequate chemistry and pharmacology/toxicology data, and any available prior human data to ensure the safety of the participants in the proposed studies. FDA must promptly review each proposed protocol and supporting data submitted with a new IND to determine whether or not the proposed study is reasonably safe to proceed. If not, FDA has 30 days after submission of the IND to notify the sponsor that the study may not proceed.[23,24]

The regulations at 21 C.F.R. § 314.50(d)(2) describe the information required from nonclinical (i.e., animal) pharmacology and toxicology studies, including 1) studies of the pharmacological actions of the drug in relation to its proposed use and/or to possible adverse effects; 2) toxicological studies related to the drug's intended clinical uses, including acute, subacute, and chronic toxicity, carcinogenicity, and local tolerance studies; 3) studies, as appropriate, of the effects on reproduction and on the developing fetus; and 4) studies of the absorption, distribution, metabolism, and excretion of the drug in animals. Some of these studies must be completed before the submission of an IND in order to evaluate safety of the first studies in humans. Additional animal studies are required to support longer durations of treatment and/or higher doses in humans.[25]

When FDA determines that animal studies show reasonable safety for administering a drug to humans for the first time and allows human studies to proceed, the first studies are generally small (phase I) studies in healthy volunteers using single low doses of the drug to test for safety and pharmacokinetics. In subsequent studies, the doses and durations of treatment are gradually

[20] *FDA History Part II: The 1938 Food, Drug, and Cosmetic Act*, FDA.gov (updated 9/24/2012).
[21] *FDA History Part III: Drugs and Foods under the 1938 Act and Its Amendments*, FDA.gov (updated 06/18/2009).
[22] 21 C.F.R. § 312.20.
[23] 21 C.F.R. § 312.23.
[24] 21 C.F.R. § 312.40.
[25] 21 C.F.R. § 312.22.

increased. Each dose level must be supported by acceptable prior animal studies of similar exposure for similar durations.[26]

Phase II studies are generally conducted in patients with the disease to be treated in order to provide preliminary evidence of a treatment effect and safety for the intended use. Phase III studies are the large adequate and well-controlled (pivotal) studies of safety and effectiveness that are required to support marketing approval. These studies must enroll enough subjects, usually hundreds, to demonstrate statistical significance when compared to a placebo or other appropriate comparator.[27]

Throughout the drug development process, there is usually significant interaction between the sponsor and FDA to ensure that each study is appropriate to meet its objectives and that the necessary animal studies have been conducted and have demonstrated reasonable safety to support the proposed human dosing. FDA has the discretion to stop development of a drug at any time by imposing a "Clinical Hold" when significant safety issues arise or when adequate information has not been provided to ensure reasonable safety of the study participants.[28]

D. FDA Review of an NDA[29]

When all necessary studies have been completed, the company must submit a New Drug Application (NDA) to FDA, including the study results and the supporting data, in order to gain marketing approval for the product. FDA reviews the data during a designated period of time, usually 8 to 12 months from the time of submission. To support approval of the NDA, the data must provide substantial evidence of efficacy, reasonable evidence of safety, and data showing that the benefits outweigh the risk of using the product. If the evidence is not adequate, FDA will not approve the product for marketing.[30]

FDA does not rely solely on information provided by the applicant, and does its own independent review of the information provided. The data submitted in an NDA are reviewed and analyzed by multi-disciplinary teams, consisting of chemists, biopharmaceutical experts, pharmacologists/toxicologists, medical officers, statisticians and other experts, as needed. Each reviewer provides expertise in the respective discipline, and multi-disciplinary evaluation of all issues contributes to the final decisions regarding product approval. Final approval decisions are largely driven by clinical perspective on safety and effectiveness provided by the medical officer, typically a medical doctor familiar with the indication and the use of similar medical products, bringing their medical training, education, and experience to bear on that process. The clinical perspective includes consideration of the severity, seriousness, prevalence, and public health significance of the disease state and the availability and relative risks and benefits of alternative treatments in reaching a determination of reasonable safety and effectiveness.

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[26] 21 C.F.R. §§ 312.21, 312.23.
[27] 21 C.F.R. § 312.21.
[28] 21 C.F.R. §§ 312.23, 312.42.
[29] *The Drug Development Process, Step 4: FDA Review*, FDA.gov (updated 06/24/2015).
[30] 21 C.F.R. § 314.125.

E. Drug Labeling Review and Approval

The sponsor is required to submit draft labeling in the NDA. All expert disciplines review the draft for accuracy and adequacy, taking into account the labeling of similar, previously-approved products. FDA revises the labeling, as necessary, to ensure that the proposed labeling accurately summarizes the clinical data and includes adequate directions for use and warnings about risks associated with use of the product. FDA communicates and discusses its revisions with the sponsor. Final authority on specific labeling text resides with FDA. If FDA determines that specific language is needed to ensure safe and effective use of the product and the sponsor refuses, FDA will not approve the application. The labeling for the marketed product must be identical to that approved by FDA and, with certain exceptions, may not be changed without the approval of FDA.[31,32] In addition, when reviewing any supplemental application, FDA generally considers the entire label and may withhold approval of the application until requested changes to any portion of the label have been made.

As set forth in the regulations, the purpose of the label is to provide a summary of the essential scientific information needed to inform clinicians in their assessment of the risks and benefits of the product and to guide its safe and effective use.[33] Labeling is not intended to be a dispositive treatise of all possible data and information about a drug. The Act permits labeling statements with respect to safety only if they are supported by scientific evidence and are not false or misleading.[34]

Prior to 2006, a label was required to warn of "serious hazards" for which there was "reasonable evidence of an association."[35] In January 2006, FDA issued the Physician Labeling Rule (PLR). Under the PLR, warnings are only required for "clinically significant hazards" for which there is "reasonable evidence of a *causal* association."[36]

Labels are developed, maintained, and updated in collaboration between the manufacturer and FDA, which at all times maintains final authority over the labeling. The manufacturer is responsible for ensuring that the product label remains appropriate for guiding the safe and effective use of the product. When newly acquired information creates the need for label changes, the company must submit a supplemental application to FDA under 21 C.F.R. § 314.70(b)—usually a Prior Approval Supplement (PAS)—requesting approval of the proposed changes.[37] If there is no significant new safety information, a labeling change is generally not justified.

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[31] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3,968 (Jan. 24, 2006).
[32] 21 C.F.R. § 314.70.
[33] 21 C.F.R. § 201.56(a)(1).
[34] *Final Rule: Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs*, 44 Fed. Reg. 37,443 (June 26, 1979).
[35] 21 C.F.R. § 201.57(e) (current version at § 201.57(c)(6)).
[36] 21 C.F.R. § 201.57(c)(6).
[37] *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2,848 (Jan. 16, 2008).

An alternate mechanism, the Changes Being Effected (CBE) supplement described in 21 C.F.R. § 314.70(c)(6), may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction for which new information provides evidence of a causal association satisfying the standard for inclusion in the labeling under 201.57(c). Under this provision, the company may initiate certain labeling changes prior to FDA review and approval of the supplemental application. However, if FDA disapproves the supplemental application, it may order the manufacturer to cease distribution of the product with the labeling change. The January 24, 2006 Final Rule and Notices on Content and Format of Labeling for Human Prescription Drug and Biological Products states that "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the Act."[38,39] The FDA will reject CBE supplements unless the evidence of a causal association satisfies the standard for inclusion in a label.[40]

F. Postmarketing Safety Reporting

After approval of the NDA, both FDA and the manufacturer have a responsibility to continue to monitor the safety profile of the product. One component of good pharmacovigilance undertaken by both FDA and the manufacturer is the collection and evaluation of spontaneous adverse event reports. Such reports may be directly submitted to FDA through its MedWatch program or to the manufacturer, or both. Drug companies are required to keep records of adverse events that are reported with the use of their products and to report them to FDA.[41]

FDA considers postmarketing safety information obtained through its own database, postmarketing studies and literature, and evaluations by the Office of Surveillance and Epidemiology, along with information provided by the manufacturer. The manufacturer provides information to FDA from multiple sources, including its spontaneous adverse event reporting, literature sources, and post-marketing safety and surveillance studies. Industry standards for good pharmacovigilance go beyond FDA requirements and suggest that companies perform their own ongoing evaluations of safety information and provide that information to regulatory bodies. Upon receipt of safety information from any source, FDA must weigh the risks, benefits, and available alternatives, and ultimately ensure that the benefits of the drug outweigh the risks.[42]

Even with thorough and rigorous risk assessment during product development, some adverse events, particularly rare adverse events, will not be observed in clinical trials. Postmarketing risk assessment, including data collection from spontaneous reporting and safety surveillance studies, plays an important role in evaluating and characterizing a product's risk profile after approval.[43]

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[38] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3,968 (Jan. 24, 2006).
[39] *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2,848 (Jan. 16, 2008).
[40] 21 C.F.R. § 314.70(c)(7).
[41] 21 C.F.R. § 314.80.
[42] *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*, FDA.gov (updated 11/04/2009)
[43] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM250783.pdf.

While spontaneous case reports play an important role in postmarketing safety, they have significant limitations. These reports may be submitted by anybody, including healthcare professionals, patients, attorneys, family members, or others. Information in adverse event reports is anecdotal, not medically verified, and is limited to whatever the reporter provides. Information necessary to interpret the event from a medical perspective, including patient characteristics, comorbidities, interval between initial exposure and diagnosis, and any results of diagnostic testing, is generally missing. For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. The report establishes only a temporal association between the event and use of the drug.[44]

Furthermore, incidence rates cannot be calculated from spontaneous adverse event reports or case series, as neither the size and characteristics of the exposed population nor the percentage of all events that are reported are known, and it is impossible to control for confounding variables in the analysis of adverse event reports. Underreporting is also known to impede the analysis of spontaneous adverse events. However, the degree of underreporting varies according to factors such as the degree of publicity surrounding a drug, the extent to which the drug is used in the US population, and the degree to which the product has been marketed.[45,46,47,48,49] Studies attempting to quantify the extent of underreporting tend to predate FDA's use of a standard form beginning in 1993, which has led to a tripling of the number of reports received.[50]

FDA regulations lay out requirements for pharmaceutical companies with regard to reporting postmarketing safety data, including data it receives from adverse event reports. Serious events — i.e., those that are life-threatening or result in death, hospitalization, disability or permanent damage, or a congenital anomaly — whether they are domestic or foreign, must be reported to FDA within 15 days from the time they are known by the company, *unless* they are identified in the label as an event associated with the drug.[51,52] Events identified in the label as associated with the drug are considered "listed."[53]

Other adverse events must be recorded in a company database and reported to FDA in periodic safety reports submitted quarterly for the first 3 years after approval and annually thereafter. In some cases, FDA may extend or re-establish the requirement for quarterly reports or require

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[44] *Id.*
[45] *Id.*
[46] Adverse Event Reporting System (AERS), Office of Pharmacoepidemiology and Statistical *Science, Brief Description with Caveats of System* (July 18, 2015).
[47] Hazell L and Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006; 29(5):389-396.
[48] Lopez-Gonzalez E et al. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009; 32(1):19-31.
[49] McAdams M et al. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. Pharmacoepidemiol Drug Saf.. 2008; 17(3):229-39.
[50] *Id.*
[51] 21 C.F.R. § 314.80.
[52] *Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2001), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM080538.pdf.
[53] 21 C.F.R. § 314.80(a).

reports at different times. FDA regulations set forth specific requirements for the content and format of these Periodic Adverse Drug Experience Reports (PADERS).[54] However, companies may request a waiver to allow them to use different formats specified for global reporting, including the Periodic Safety Update Report (PSUR)[55] or, more recently, the Periodic Benefit-Risk Evaluation Report (PBRER).[56] Periodic reporting requirements in the US, except for information regarding 15-Day Safety Alert reports for serious unlisted adverse events, do not apply to foreign marketing experience,[57] though in keeping with industry standards for pharmacovigilance many companies include foreign postmarketing experience in their periodic reporting.

A safety signal is a concern about an excess of adverse events associated with product use compared to what would be expected in the population at issue. The expected rate is usually a background rate derived from sources such as national health statistics, published medical literature, and/or ad hoc studies of subpopulations, using large automated databases or ongoing epidemiologic investigations. Safety signals may arise from analysis of spontaneous reports of adverse events, preclinical data, clinical studies and/or events associated with other products in the same class. Single case reports are rarely sufficient to allow any conclusions. A signal does not itself show that a drug causes a particular event, nor does a signal alone show a change in the drug's safety profile. Signals indicate the need for further investigation, which may or may not lead to the conclusion that the product causes the event.[58]

Pharmacoepidemiologic studies play an important role in postmarketing safety surveillance, by evaluating an identified safety signal. Unlike spontaneous case reports, well-designed postmarketing surveillance studies can provide information on comparative risk, incidence of rare adverse events, risk factors for those events, and/or the rate of serious long-term complications associated with such events. Such studies can provide FDA and the sponsor with important, objective, medically verified, clinically relevant information about safety and efficacy that cannot be obtained from spontaneous adverse event reports. However, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results due to the effects of bias, confounding, or effect modification. Therefore, it is almost always prudent to conduct more than one study in more than one environment and even use different designs. Agreement of the results from a variety of studies helps to provide reassurance that the observed results are robust.[59]

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[54] *Id.*

[55] *Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2001), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM080538.pdf.

[56] *Guidance for Industry: Providing Postmarket Periodic Safety Reports in the ICH E2C (R2) Format (Periodic Benefit-Risk Evaluation Report)*, U.S. Department of Health and Human Services, Food and Drug Administration (Apr. 2013), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm346564.pdf.

[57] 21 C.F.R. § 314.80(c)(2)(iii).

[58] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005)

[59] *Id.*

IV. Unintended Pregnancy & Contraception

Before 1960, women in the United States had limited options for pregnancy prevention. These included sexual abstinence, the rhythm method (without adequate information to plan the right timing), withdrawal, various precursors to modern condoms (earlier versions made from linen or animal intestines, and later ones made from rubber), diaphragms, cervical caps, foams, douches made from various household products presumed to be spermicides, and IUDs. Even sterilization was not generally available.[60] The available methods generally were not very effective, and some were unsafe. Women too often resorted to unsafe illegal or self-induced abortions when these methods failed, and the results were too often disastrous, resulting in sepsis and death or infertility.[61]

Contraceptive methods have improved over the years. The availability of oral contraceptives, a method that was easy to use and generally very well tolerated, was a catalyst for increasing availability of contraception in general; however, concerns about thrombosis, heart disease, and cancer highlighted the need for additional contraceptive options that were effective, easy to use, and reversible.

Intrauterine devices provided a valuable alternative to oral contraceptives and gained popularity in the 1970s. However, the highly-publicized and serious complications with the Dalkon shield, including septic abortions and deaths, caused all IUDs to fall out of favor with both providers and patients in the United States. The IUD is one of the most effective, safe, and economic methods of contraception, and is used by more women worldwide than any other reversible method of birth control.[62,63,64] Yet, when Mirena was approved in 2000, less than 1% of women in the US used an IUD.[65]

Another long-acting reversible contraceptive (LARC) available at the time of Mirena's approval was Norplant, a set of six levonorgestrel-releasing capsules intended to be implanted under the skin to release levonorgestrel slowly into the bloodstream over a period of five years.[66] Norplant was approved in the US in December 1990 after 25 years of development. Marketing began in early 1991, and within 2 years, over one million women had become Norplant users. However in March 1994, negative media coverage regarding alleged problems with Norplant and initiation of lawsuits against the sole U.S. distributor, Wyeth-Ayerst, began to affect the market. By 1996, insertions had decreased by 90 percent, and annual sales had dropped from $141 million in the first year to only $3.7 million. By August 1997, 50,000 US women were reported to have sued Wyeth-Ayerst, alleging that it failed to adequately warn users of complications or potential side effects. The alleged injuries generally fell into three categories: capsule displacement and

[60] A History of Birth Control Methods, Planned Parenthood Federation of America (Jan. 2012).
[61] Gold RB. Lessons from before Roe: will past be prologue? Issues Brief (Alan Guttmacher Inst). 2003; (5):1-4.
[62] ACOG Committee Opinion 450: Increasing use of contraceptive implants and intrauterine devices to reduce unintended pregnancy. Obstet Gynecol. 2009; 114(6):1434-1438.
[63] ACOG Practice Bulletin 121: Long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2011; 118:184-196.
[64] WHO. Intrauterine devices: what health workers need to know. Geneva. 1997.
[65] Branum A and Jones J. Trends in long-acting reversible contraception use among U.S. women aged 15–44. NCHS Data Brief. 2015; 188:1-7.
[66] Norplant System, Physicians' Desk Reference 1992, 2484-2488.

removal difficulties, possible levonorgestrel-related effects, and silastic-related claims, including autoimmune problems and other injuries related to the silicone elastomer tubing. By 2000, Norplant was no longer sold in the United States, having been voluntarily withdrawn by the manufacturer for reasons wholly unrelated to IIH.[67,68]

Meanwhile, the Population Council developed a new levonorgestrel implant consisting of only 2 solid rods, known initially as Norplant-2 and subsequently named Jadelle. An NDA for this product was submitted to FDA in 1995 and approved in 1996.[69] The product has been distributed in foreign countries through aid programs, but never marketed in the US.[70]

Another hormonal contraceptive implant consisting of a single rod releasing the progestin etonogestrel was approved by FDA in 2006.[71] The same implant was approved with a pre-loaded applicator device (Nexplanon) and without it (Implanon). Implanon has been discontinued, but Nexplanon remains available. The duration of effectiveness for Nexplanon is three years.

Following Mirena's introduction and positive reception among women and leaders in the field of family planning, IUDs have again emerged as one of the best options for reversible contraception. IUDs offer excellent efficacy and an excellent safety profile, and are recommended by leading public health organizations as a first line contraceptive option for most women.[72,73,74,75]

Women and their healthcare providers must make decisions regarding the use and method of contraception, considering the risks and effectiveness of the method versus the risks of pregnancy and the consequences of unintended pregnancy. Most women tend to overestimate the risk of contraceptives and to underestimate the risk of pregnancy.[76,77] In the United States, 650 women die each year from complications related to pregnancy or delivery.[78] In addition, 50,000

[67] Watkins ES. From breakthrough to bust: the brief life of Norplant, the contraceptive implant. J Womens Hist. 2010; 22(3):88-111.
[68] Harrison PF & Rosenfield A. Contraceptive research, introduction, and use: lessons from Norplant. Appendix B. 1998.
[69] *Determination That JADELLE (Levonorgestrel) Implant, 75 Milligrams, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness*, 79 Fed. Reg. 51,575 (Aug. 29, 2014).
[70] *Id.*
[71] Implanon FDA Approval Letter, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021529s000_Approv.pdf.
[72] ACOG Committee Opinion 450: Increasing use of contraceptive implants and intrauterine devices to reduce unintended pregnancy. Obstet Gynecol. 2009; 114(6):1434-1438.
[73] ACOG Practice Bulletin 121: Long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2011; 118:184-196.
[74] WHO. Intrauterine devices: what health workers need to know. Geneva. 1997.
[75] CDC. US Medical Eligibility Center for Contraceptive Use. Morbidity and Mortality Weekly Report 2010; 59(RR-4).
[76] ACOG Half of women unaware that pregnancy is more dangerous than contraception. 2013.
[77] Speidel J, et al. Pregnancy: not a disease but still a health risk. Contraception 2013; 88:481-484.
[78] *Reproductive Health, Pregnancy-Related Deaths*, Centers for Disease Control and Prevention, cdc.gov (updated 12/17/14).

women have significant maternal morbidity (SMM) in the US every year,[79] including hemorrhage, heart failure, and hysterectomy.[80] These rates of maternal morbidity and mortality are markedly higher than the rates of serious adverse events reported with the use of modern contraceptives.

Access to effective contraception is a significant public health issue, and a metric on which the United States does worse than most other developed countries. Roughly half of all pregnancies in the United States are unintended, and approximately half of those result from the inconsistent or incorrect use of contraception.[81,82] A significant percentage (roughly 40%) of unintended pregnancies end in abortion. Those pregnancies that result in unintended births are associated with poor maternal and child outcomes, including delayed prenatal care, higher rates of substance use during pregnancy, poorer health during childhood, and poorer outcomes for the mother-child relationship.[83] Women who experience an unintended birth are more likely to remain poor and less likely to reach their educational goals.[84] The best available evidence shows that long-acting reversible contraception methods such as Mirena play a key role in decreasing the rate of unintended pregnancy and abortion.[85,86]

Given the importance of preventing unintended pregnancy to improve health outcomes, the American College of Obstetricians and Gynecologists (ACOG) considers contraception to be basic, preventive health care that should be readily available and prioritized just as much as prophylactic therapies for other medical conditions.[87] ACOG, the CDC, and the American Academy of Pediatrics (AAP) all strongly encourage women's healthcare providers to consider long acting reversible contraception as first line methods of contraception for most women.[88,89,90,91] Serious complications with these methods are rare and differ little between

[79] *Reproductive Health, Pregnancy Complications*, Centers for Disease Control and Prevention, cdc.gov (updated 08/13/14).
[80] *Reproductive Health, Severe Maternal Morbidity in the United States*, Centers for Disease Control and Prevention, cdc.gov (updated 01/22/14).
[81] Peipert J, et al. Preventing unintended pregnancies by providing no-cost contraception. Obstet Gynecol. 2012; 120:1291-1297.
[82] Winner B et al. Effectiveness of long-acting reversible contraception. N Engl J Med. 2012; 366(21):1998-2007.
[83] Mosher WD, et al. Intended and unintended births in the United States 1982-2010. National Health Statistics Reports, July 2012 (updated 12/20/2012). http://www.cdc.gov/nchs/data/nhsr/nhsr055.pdf.
[84] Hoffman SD. By the numbers: the public costs of teen childbearing. The National Campaign to Prevent Teen Pregnancy Oct. 2006;1-50.
[85] Peipert J, et al. Preventing unintended pregnancies by providing no-cost contraception. Obstet Gynecol 2012; 120:1291-1297.
[86] Winner B et al. Effectiveness of long-acting reversible contraception. N Engl J Med. 2012; 366(21):1998-2007.
[87] ACOG. Contraception: A Basic Health Necessity. 2007.
[88] ACOG Committee Opinion 450: Increasing use of contraceptive implants and intrauterine devices to reduce unintended pregnancy. Obstet Gynecol. 2009; 114(6):1434-1438.
[89] ACOG Practice Bulletin 121: Long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2011; 118:184-196.
[90] WHO. Intrauterine devices: what health workers need to know. Geneva. 1997.
[91] CDC. US Medical Eligibility Center for Contraceptive Use. Morbidity and Mortality Weekly Report 2010; 59(RR-4).

adolescents and older women.[92] These are the most effective reversible contraceptives and do not require ongoing effort on the part of the user for long-term effective use. Furthermore, return of fertility is rapid after the removal of the device.[93] ACOG specifically recommends the use of Mirena in obese women, and the CDC recommends Mirena without restriction in this population.[94,95]

V. The Mirena IUD

A. Early Product Development

Mirena is a flexible T-shaped IUD containing 52 mg of levonorgestrel in a sleeve-like reservoir surrounding the stem of the "T." Approved in 2000, Mirena has been demonstrated to be effective for 5 years of use, and it has proven to be more effective in preventing pregnancy than even female sterilization.[96,97,98,99] Levonorgestrel is slowly released from Mirena into the uterine cavity for five years. The mechanisms of action of IUDs are still not fully understood. The five years of contraceptive action is more likely related to the high local concentrations in the uterus than to the low serum concentrations of levonorgestrel produced by the product. Mirena has progestational effects on cervical mucus, tubal motility and endometrial histology, all of which may contribute to its contraceptive effect.[100]

Although an IND was submitted to FDA in 1983, it was not a major focus for FDA or the sponsor over the next decade.[101] The focus of the development and regulatory approval of Mirena at that time was in Europe. Large-scale clinical trials were conducted in Europe between 1982 and 1996, following the product's initial development in Finland in the 1970s. The Finnish company Leiras Oy sponsored the first large-scale phase III trial in Europe, enrolling patients from 1982 to 1989. The product was first approved for marketing in Finland in 1990. At the time, IUDs were not in favor in the United States, and nearly all had been voluntarily withdrawn from the market for economic reasons.

Bayer and its predecessors met or exceeded regulatory standards with regard to the early development of Mirena, and worked with FDA to ensure all regulatory requirements were met. Berlex Laboratories, the US subsidiary of Schering AG, met with FDA in January 1998, when it

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[92] ACOG Committee Opinion 539: Adolescents and long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2012; 120(4):983-8.

[93] ACOG. Practice Bulletin 121: long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol 2011; 118:184-196.

[94] ACOG Practice Bulletin 73: Use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. 2006; 107(6):1453-1472.

[95] CDC. US Medical Eligibility Center for Contraceptive Use. Morbidity and Mortality Weekly Report 2010; 59(RR-4).

[96] Trussell J. Contraceptive failure in the United States. Contraception. 2011; 83(5):397-404.

[97] MIR_INDNDA_00322869-00322899.

[98] MIR_BSR-R_00317166-00317275.

[99] A smaller version named Skyla was approved on January 9, 2013 for up to 3 years of continuous use.

[100] MIR_INDNDA_00322869- 00322899.

[101] The holders of the Mirena IND and NDA, have, in sequence, included the Population Council; Leiras Oy; Berlex Laboratories, as a subsidiary of Schering AG; and Bayer HealthCare Pharmaceuticals.

was acquiring the US IND from the Population Council. FDA required data from at least 200 women who completed 5 years of product use at valid sites, and at least 35,000 to 40,000 total women-months of data.[102] Berlex submitted NDA 21-225 to FDA on February 2, 2000. As of March 27, 2000 the product had already been approved for marketing in 52 countries, with no market withdrawals.[103]

The Mirena NDA included reports of three phase III contraception trials conducted in Finland and Sweden from 1982 to 1996 enrolling 2,339 subjects, with a total overall exposure of 92,129 woman-months and a total of 877 women completing 5 years of use. These included 663 women (more than three times the FDA requirement) completing five years of use in qualified[104] sites with 64,136 woman-months exposure to Mirena from those sites (at least 25,000 woman-months more than the FDA requirement).[105] In all respects, the company exceeded FDA requirements for the conduct of pre-market approval studies. As described below, the results of those studies were sufficient to support the approval of Mirena as safe and effective for contraceptive use.

Levonorgestrel is one of the oldest and most widely studied synthetic progestins used in hormonal contraception. The systemic concentration of levonorgestrel produced by Mirena is only approximately 10% of that produced by an oral contraceptive containing 0.1 mg of levonorgestrel and half that produced by the Norplant system, and thus the longstanding use of products with much higher systemic levels of levonorgestral provided reassurance to the company and FDA that the comparatively lower levels present in Mirena users would not present a safety concern.[106] The contraceptive efficacy of Mirena is based primarily on the local effect of levonorgestrel in the uterus, and the local endometrial concentrations of levonorgestrel are over 100 times higher in Mirena users than in users of oral contraceptives containing 0.25 mg levonorgestrel.

When the Mirena NDA was submitted to FDA, there were two other FDA-approved IUDs on the market, as well as numerous other contraceptive products containing the drug levonorgestrel or other progestins. Given the long history of safe and effective use of these products in humans, there was limited need for pre-clinical studies of Mirena. Prior animal and human studies have shown these products to be safe. In vivo and in vitro genotoxicity studies were conducted on the levonorgestrel IUD and its components and showed no toxicity. Studies of implants in rats and

[102] MIR_JR_00001106-00001155.
[103] *Id.*
[104] Per the NDA 21-225 Submission, MIR_INDNDA_127646, at -128253, the largest study (Report B075, conducted under Protocol 61540-8216) began in September 1982, before the first 2 pan-European standards of good clinical practice were established in the late 1980s. Therefore, Leiras Oy had not compared the entries on the case report forms (CRFs) and source documents as required by international guidelines in place at the time of the NDA submission. To compensate for this, retrospective monitoring of the levonorgestrel IUS subjects was performed under a new Protocol LE102-98042 (Report AY99), including on-site source data verification of the CRF entries against the source documents. The FDA review of the NDA relied upon data from qualified sites, defined as study sites for which source data and informed consent were verifiable. Data from unqualified sites was presented where informative but the reviewer did not rely upon that data for safety and efficacy assessments.
[105] MIR_JR_00001106-00001155.
[106] MIR_AC_398249, at -254.

cynomolgus monkeys for 6 and 9 months, respectively, showed no toxicity. Studies in pregnant rabbits showed no embryo or maternal toxicity.[107,108]

The record demonstrates that Bayer and its predecessors met or exceeded their regulatory responsibility in the development of Mirena. Bayer proactively sought guidance from FDA prior to the NDA submission and during the review, followed FDA's recommendations and requests, and fulfilled the postmarketing commitments requested by FDA. The company also provided pharmacokinetic data, which FDA accepted, supporting the dosing of Mirena for contraceptive use.

Bayer included data from foreign clinical trials in its NDA. It is not unusual for foreign studies to be used to support approval in the United States. An application based solely on foreign clinical data may be approved by FDA as long as the foreign data are applicable to the U.S. population and U.S. medical practice.[109] FDA's approval of Mirena is evidence that FDA considered the European study populations to be adequately similar to the American population with regard to contraceptive trials. As recommended by FDA,[110] Bayer discussed its use of foreign data with FDA in a presubmission meeting.[111] FDA was thus well aware that Bayer's application was based solely on foreign clinical data. If FDA believed that the European study populations were not applicable to the US population and US medical practice, it would have been obligated not to approve the application.[112]

B. Safety & Efficacy of Mirena

It is my opinion that the information submitted in the NDA was sufficient to support the safety and efficacy of Mirena for contraception. Mirena was proven to be highly effective and well tolerated throughout five years of continuous use.

The efficacy of Mirena was demonstrated by a one-year Pearl Index of 0.19 (95% confidence interval 0.02, 0.70) pregnancies per 100 woman-years and a five-year Pearl Index of 0.08 (0.02, 0.23) pregnancies per 100 woman-years over 5 years of continuous use. Perfect and typical use Pearl Indices are roughly equivalent for Mirena. These results, calculated from 1,169 women who were between 18 and 35 years of age at baseline in the clinical studies, are substantially lower than the published Pearl Index rates for most other approved contraceptive products, particularly when typical use is taken into account (0.1 for perfect use of birth control pills vs. 5 with typical use, 6 for the diaphragm vs. 20 with typical use, 3 for the male condom vs. 14 with typical use, 0.6 for the copper T 380A IUD, and 85 for use of no birth control method).[113]

In the pivotal trials, 78% of Mirena users continued use at one year, and 45% at 5 years, comparable to the estimated continuation rates at one year for other contraceptive methods (72%

[107] MIR_AC_00144459-00144474.
[108] MIR_JR_00001106-00001155.
[109] 21 C.F.R. § 314.106(b)(1).
[110] 21 C.F.R. § 314.106(c).
[111] MIR_HC_238038, at -045.
[112] 21 C.F.R. § 314.106(b).
[113] MIR_JR_00001106-00001155.

for birth control pills and 78% for the ParaGard T 380A copper IUD).[114] The pregnancy rates at 1 year after removal of the levonorgestrel IUD in two published studies of about 250 women desiring pregnancy ranged from 79 to 84%, comparable to general pregnancy rates in women not using contraception. The median time from removal to pregnancy was 4 months for levonorgestrel IUD users (N=60) in one study.[115] Thus, Mirena was shown in the clinical trials to be highly effective, with high rates of continuation at one and five years and a rapid return to fertility on discontinuation.

Clinical trials also demonstrated the safety of Mirena. There were no deaths related to Mirena use in the clinical trials. Serious events that were reported in the clinical trials[116] included pelvic inflammatory disease, ovarian cysts, and ectopic pregnancy, all at a rate at or lower than that seen in the general population; and myocardial infarction in one 42-year old woman with pre-existing hypertension.[117] No cases of IIH were reported in clinical trials prior to FDA approval. The overall rate of expulsion was 3.21% at 1 year, and 5.21% over 5 years, similar to the rate of 5.7% reported in the labeling of ParaGard T 380A copper IUD for the first year of use.[118]

Changes in bleeding patterns are to be expected with use of any IUD. With use of Mirena, increased days of bleeding and spotting are expected in the first 3 months, followed by only a few days of bleeding or spotting after the first year, with 21% of women having no bleeding at all after the first year of use, and an overall increase in hemoglobin and serum ferritin levels was observed in clinical trials.[119] Decreased bleeding is often considered a desirable effect.

On October 1, 2009, an efficacy supplement (S-027) for Mirena was approved by FDA for the indication of treatment of heavy menstrual bleeding, for women who choose to use intrauterine contraception as their method of contraception. Menorrhagia, or heavy menstrual bleeding, is a leading cause of iron deficiency anemia in women, requiring treatment with iron supplementation, and sometimes blood transfusions and/or surgical management such as hysterectomy, myomectomy, endometrial ablation, or uterine artery embolization. It may also have a significant impact on quality of life, including the ability to work, go to school, or perform normal daily activities. Available treatments for heavy menstrual bleeding previously included systemic hormonal medications, including oral contraceptives, with their associated risks, and the aforementioned major surgical procedures with their associated risks including loss of fertility.

Prior to submission of this efficacy supplement to FDA, the levonorgestrel IUD had been approved for the indication of "treatment of idiopathic menorrhagia" in over 100 countries. The clinical studies that supported this use showed that it decreases the amount and duration of menstrual bleeding, with an increase in hemoglobin and serum ferritin levels in women who previously had normal menstrual bleeding as well as in women with menorrhagia.[120,121] Women

[114] *Id.*
[115] *Id.*
[116] Serious adverse events in clinical trials are reported regardless of a causal relationship to the drug.
[117] MIR_JR_00001106-00001155.
[118] *Id.*
[119] *Id.*
[120] MIR_INDNDA_254000.

using Mirena for heavy menstrual bleeding may avoid alternative surgical treatments (including hysterectomy, endometrial ablation or resection, or uterine artery embolization) or systemic hormonal therapies, all of which have common side effects of nausea and/or headaches and a rare risk of serious thromboembolic events. The local release of a progestin in the endometrial cavity, combined with lower levels of circulating hormone, results in fewer systemic adverse events compared with systemic formulations. Progestins, including Mirena, also have a protective influence on the endometrium, lowering the risk for endometrial hyperplasia and cancer.[122]

C. Safety and Efficacy of Mirena Among Obese Women

In a 2006 Practice Bulletin, the American College of Obstetricians and Gynecologists specifically recommended the use of progestin-only and intrauterine methods of contraception for obese women.[123] ACOG noted that combined oral contraceptives and obesity are independent risk factors for venous thromboembolism (VTE), and that women with a BMI over 25 who also use combined oral contraceptives have a 10-fold higher risk of VTE. ACOG further noted a higher risk of oral contraceptive failure in obese women than in women with a normal BMI.[124] ACOG concluded, "Because obese women experience an elevated risk for dysfunctional uterine bleeding and endometrial neoplasia, use of the levonorgestrel intrauterine system may represent a particularly sound choice for obese women."[125]

The Mayo Clinic's Department of Obstetrics & Gynecology similarly advises that progestogen-only and non-hormonal contraceptives are "preferred methods of contraception for women who are obese," that intrauterine devices are effective at preventing unintended pregnancies regardless of BMI, and that intrauterine devices "may be the ideal first option" for women with higher BMIs.[126]

VI. Adequacy of the Mirena Label

Plaintiffs in this litigation allege that Mirena caused them to develop IIH, and that the Mirena labeling is inadequate because it does not contain a warning about IIH. Based on my review of the regulatory record, it is my opinion that no IIH warning was necessary. At all times since NDA approval in December 2000, the Mirena prescribing information has adequately warned of the known risks associated with the use of Mirena. These risks did not, and do not, include IIH. In this section, I will first discuss IIH, its diagnosis, and its incidence rates in the relevant populations. I will then demonstrate the adequacy of the Mirena label based on a review of the relevant regulatory materials.

[121] MIR_INDNDA_253743.
[122] MIR_AC-R_00031243-00031364.
[123] ACOG Practice Bulletin 73: Use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol 2006; 107(6):1453-1472.
[124] *Id.*
[125] *Id.*
[126] Mamach M et al. Current Issues in Contraception. Mayo Clinic 2013; 88(3):295-299.

A. Overview of Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension — sometimes called pseudotumor cerebri, or benign intracranial hypertension — is a disorder defined by elevated intracranial pressure with normal cerebrospinal fluid (CSF) composition and no identifiable cause of intracranial hypertension. The most common symptoms of IIH are headache, visual disturbances, pulsatile noises in the head, and a finding of papilledema on eye examination, indicating swelling of the optic nerve. In some cases cranial nerve deficits are found.

IIH is not the only cause of intracranial hypertension. Other primary causes include brain tumor, trauma to the brain, non-traumatic intra-cerebral hemorrhage, infection, and hydrocephalus. Secondary causes arise from systemic conditions, including airway obstruction, hypoxia or hypercarbia (hypoventilation), hypertension (pain/cough) or hypotension (hypovolemia/sedation), posture (head rotation), fever, seizures, drug and metabolic effects, thrombosis, and others. A third category is postoperative effects.[127]

Thus, IIH is often considered a diagnosis of exclusion, with diagnosis made according to the modified Dandy criteria:

- Symptoms and signs of increased intracranial pressure (headache, transient visual obscurations, pulse synchronous tinnitus, papilledema, visual loss);
- No other neurologic abnormalities or impaired level of consciousness;
- Elevated intracranial pressure with normal CSF composition;[128]
- Neuroimaging showing no etiology for intracranial hypertension;
- No other cause of intracranial hypertension apparent.[129]

For many patients, IIH is a self-limiting condition that resolves either spontaneously or in some patients soon after their initial lumbar puncture, which allows for the removal of CSF.[130] Typical treatments include weight loss, lumbar puncture, and acetazolamide.[131]

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[127] Rangel-Castillo L et al. Management of Intracranial Hypertension. Neurol Clin. 2008; 26(2):521-541.

[128] In the average adult, the total intracranial volume is 1450 mL, including brain volume of 1300 mL, 65 mL of CSF, and 110 mL of blood. Normal intracranial pressure (ICP) is less than 10 to 15 mm Hg (7.5-20 cm H_20) for adults. The skull allows for very little expansion in the volume of its contents, so that when any of its contents expand, the intracranial pressure increases. When ICP is 20-30 mm Hg, mild intracranial hypertension is present. ICP levels greater than 20 to 25 mm Hg require treatment in most circumstances, and sustained ICP values above 40 mm Hg indicate severe, life-threatening intracranial hypertension. Rangel-Castillo L et al. Management of Intracranial Hypertension. Neurol Clin. 2008; 26(2): 521–541.

[129] Lee GL and Wall M. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Clinical Features and Diagnosis. UpToDate 2015.

[130] Biousse V et al. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2012; 83(5):488-494.

[131] Lee GL and Wall M. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Prognosis and Treatment. UpToDate 2015.

Although the overall annual incidence of IIH was estimated to be approximately 1 per 100,000 person-years in the general population, based on data from 30 years ago, IIH is markedly more common in women of childbearing age (approximately 3.5 per 100,000), and most common in the subset of those women who are overweight, obese, or have experienced recent weight gain. One study found that women between ages 20 and 44 who were 10% or more over ideal body weight had an incidence rate of 14.85 per 100,000 woman-years, and that similarly aged women who were 20% or more over ideal weight had an incidence rate of 19.3 per 100,000 woman-years.[132] Other studies have yielded similar findings, and a prospective study of 50 patients diagnosed with IIH found that 94% were obese.[133] Epidemiology studies have consistently found excess weight to be a risk factor for developing IIH, and recent weight gain appears to be an independent risk factor.[134,135,136] As the U.S. population has become heavier in the decades since the original 1 in 100,000 person-years incidence rate was calculated, one would expect a higher overall annual incidence rate of IIH in the general population. Interestingly, while systemic estrogen levels tend to be higher in obese women, progesterone levels tend to be lower.[137]

Although IIH is by definition idiopathic, a number of systemic diseases, drugs, vitamin deficiencies and excesses, and hereditary conditions have been reported in association with IIH. However, most patients with IIH do not have one of these conditions, and the true link between these conditions and IIH is uncertain. In case control studies, the prevalence of menstrual irregularities, pregnancy, antibiotic use, iron deficiency anemia, thyroid dysfunction, and oral contraceptive use were no different among cases and controls.[138] Obesity and weight gain are the only demonstrated risk factors for IIH. Increasing levels of BMI and percentage weight gain have been shown to be associated with progressively greater risk of IIH.[139]

B. Because there Was No Reasonable Evidence of an Association Between Mirena and IIH When the Mirena NDA Was Approved in 2000, the 2000 Mirena Launch Label Was Adequate

Dr. Ross argues that the Mirena label should have included an IIH warning by virtue of the fact that Norplant's label included an IIH warning, and he suggests that the Norplant IIH warning served as reasonable evidence of an association between Mirena and IIH. This argument (1)

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[132] Durcan P et al. The incidence of pseudotumor cerebri: population studies in Iowa and Louisiana. Arch Neurol. 1988; 45:875-877.
[133] Wall M & George D. Idiopathic intracranial hypertension. A prospective study of 50 patients. Brain. 1991; 114:155-180.
[134] Lee GL and Wall M. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Epidemiology and Pathogenesis. UpToDate 2015.
[135] Daniels AK et al. Profiles of obesity, weight gain and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). American Journal of Ophthalmology 2007; 143,4:635-641.
[136] Ko MW et al. Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study. Neurology. 2011; 76:1564-1567.
[137] Yeung EH. Adiposity and sex hormones across the menstrual cycle: the BioCycle Study. Int J Obes. 2013; 37(2):237-243.
[138] Lee GL and Wall M. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Epidemiology and Pathogenesis. UpToDate 2015.
[139] Daniels AK et al. *Profiles of Obesity, Weight Gain and Quality of Life in Idiopathid Intracranial Hypertension (Pseudotumor Cerebri).* American Journal of Ophthalmology 2007; 143,4:635-641.

misstates the applicable labeling requirements, (2) relies upon an incorrect assumption that Norplant and Mirena are comparable; (3) overstates the strength of the association between Norplant and IIH; and (4) overlooks the fact that early Mirena data did not support a relationship between IIH and Mirena.

1. Bayer Could Not Simply Incorporate All Warnings Listed in the Norplant Label to Satisfy Its Labeling Obligations

Dr. Ross's allegation that the 2000 Mirena launch label should have included a warning about the risk of IIH because the label for Norplant, another hormonal contraceptive, contained such a warning is not supported by any regulatory requirements or standards. Sponsors are under no general obligation to incorporate warnings from other medications, regardless of whether those medications are broadly in the same class (here, progestin-containing contraceptives), and indeed it would be quite unwise to simply copy over labels from other medicines without an independent evaluation of the scientific evidence available for the medicine at issue. To be sure, manufacturers generally consider the warnings of other similar medications and make a reasoned determination whether their own medication should include similar language based upon their knowledge of that medication, but the primary objective is to make an assessment of the medicine at issue. Similarly, Dr. Ross provides no support for his claim that in the absence of clinical studies disproving the hypothesis that Mirena caused IIH, Bayer was obligated to include an IIH warning in the label. For one, given the rarity of IIH, it would have been impossible to design a clinical trial to disprove the hypothesis that Mirena causes IIH. FDA has recognized that "clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000."[140] Even in the population most at risk for IIH, obese women of childbearing age, IIH occurs only in 1 out of every 5,000 women.[141] More importantly, Dr. Ross's claim runs counter to FDA's longstanding position of discouraging over-warning, which can cause important evidence-based warnings in the label to be overlooked or deny populations access to a beneficial drug.[142,143,144]

Bayer appropriately considered the labels of other products when developing the 2000 Mirena label, and internal company communications demonstrate that the original Mirena label was

[140] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM250783.pdf.

[141] Durcan P et al. The incidence of pseudotumor cerebri: population studies in Iowa and Louisiana. Arch Neurol. 1988; 45:875-877.

[142] *Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs*, 44 Fed. Reg. 37434 (June 26, 1979) ("The Commissioner believes that including theoretical hazards as contraindications in drug labeling would cause that very important section of the labeling to lose its significance.").

[143] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922 (Jan. 24, 2006) ("Overwarning, just like underwarning, can . . . have a negative effect on patient safety and public health. . . . FDA believes that including relative or hypothetical hazards diminishes the usefulness of the [contraindications] section.").

[144] *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2848 (Jan. 16, 2008) ("[I]nclusion of speculative or hypothetical risks, could . . . decrease the usefulness and accessibility of important information by diluting or obscuring it. As FDA has stated, labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance.").

modeled on the labels for other marketed IUDs.[145,146] As noted above, when seeking to develop a new label, it is reasonable for a manufacturer to consult the labels of similar already-approved medications. Although Bayer considered the label for Norplant (a subdermal device delivering a systemic dose of levonorgestrel (LNG)), IUDs were the primary references used to develop Mirena labeling.[147,148,149,150,151,152,153] Using the IUD labels as models for Mirena made ample sense, given that Mirena is an IUD. In fact, the FDA medical reviewer noted that Mirena's "[r]ecommended warnings include the warnings that are currently on the USA labels for the other two USA-approved IUDs."[154]

While it was appropriate to consult the Norplant label as needed, no regulation obligated Bayer to adopt the language from Norplant's label in its entirety. Instead, Bayer appropriately decided that language from the Norplant labeling was to be used only where scientific evidence showed its applicability not only to Norplant, but also to Mirena,[155] and that the focus should be on the risks associated with the Mirena intrauterine product itself, rather than on levonorgestrel in general.[156] For example, although the Norplant label contained a precaution regarding autoimmune disease related to the use of silicone, Bayer decided that "[f]rom a medical/toxicological perspective there is no reason to assume that the silicone tubing of Mirena might induce autoimmune disease."[157] Consequently, the proposed Mirena label that was submitted to FDA did not contain such a precaution.

Bayer did include the 1997 Norplant label as part of its Mirena NDA submission.[158] Despite the submission of the FDA-approved Norplant label, and despite the IIH warning language in the Norplant label, FDA did not require Bayer to discuss IIH in the Mirena label, even though it would have been within FDA's power to mandate the inclusion of such language if it thought such a warning was scientifically appropriate.

2. Basic Differences Between Mirena and Norplant Argue Against Automatically Importing Norplant Warnings Into the Mirena Label

Mirena is a different product than Norplant, with a different mechanism and a different safety profile. Mirena provides its contraceptive effect primarily by acting locally in the uterus, whereas Norplant is implanted under the skin of the arm to deliver levonorgestrel through the bloodstream. Therefore, whereas Norplant acts systemically, Mirena primarily acts locally within

[145] MIR_JR_00186051.
[146] MIR_JR_00186066.
[147] MIR_JR_00186596.
[148] MIR_JR_00186051.
[149] MIR_JR_00186491.
[150] MIR_JR_00186518.
[151] .MIR_JR_00186596.
[152] MIR_JR_442929.
[153] MIR_PSEU_00530579.
[154] MIR_AC_398249, at -254.
[155] MIR_JR_00186491.
[156] MIR_JR_00186051.
[157] MIR_JR_442929.
[158] MIR_INDNDA_53366, at -55897.

the uterus.[159] There is no requirement for a locally-acting levonorgestrel intrauterine system to be labeled with all of the same warnings and contraindications that were in the label of a levonorgestrel subcutaneous implant.

The average daily dose of LNG released by Norplant is also approximately three to four times higher than that released by Mirena. As the 1996 Norplant label states, "the dose of levonorgestrel provided by the NORPLANT SYSTEM is initially about 85 mcg/day followed by a decline to about 50 mcg/day by 9 months and to about 35 mcg/day by 18 months with a further decline thereafter to about 30 mcg/day."[160] By contrast, the Mirena label explains that "[l]ow doses of LNG are administered into the uterine cavity with the Mirena intrauterine delivery system. The initial release rate is approximately 20 mcg/[day] over the first 3 months tested (day 0 to day 90). It is reduced to approximately 18 mcg/day after 1 year and then decreases progressively to approximately 10 mcg/day after 5 years."[161]

Finally, and relatedly, mean LNG blood concentrations are almost twice as high among Norplant users. In patients using Norplant, LNG levels at 12 months are 327±119 pg/mL, and LNG levels at 60 months are 258±119 pg/mL.[162] Mirena LNG concentrations, by contrast, are 180±66 pg/mL at 12 months and 159±59 pg/mL at 60 months.[163] The fact that a small number of Norplant users with below-average LNG levels may have approximately the same LNG concentrations as a small number of Mirena users with above-average LNG levels obscures the simple fact that most Norplant users will have higher LNG concentrations than most Mirena users.

Dr. Ross insists that the LNG blood concentrations for Mirena and Norplant are "comparable," despite the fact that the average Mirena LNG level is 55% of Norplant at 12 months. This assertion is belied by his statement that Skyla — which has an average LNG level of 43% of Mirena at 12 months[164] — generates "considerably lower LNG blood concentrations" than Mirena.

3. Norplant's IIH Warning Was Based on a Small Number of Spontaneous Adverse Event Reports

Not only are Mirena and Norplant substantially different products, the evidence supporting Norplant's IIH warning is extremely tenuous.

Records indicate that IIH language was added to the Norplant label due entirely to a handful of spontaneous adverse event reports. According to records of a telephone conversation with Dr. Lisa Rarick of FDA on November 10, 1992, Wyeth indicated that it would be submitting proposed labeling for Norplant to address spontaneous reports of IIH that had been received from Norplant users.[165] A letter from five days later confirmed that Wyeth "would be submitting

[159] 2014 Mirena Label ("Mirena has mainly local progestogenetic effects in the uterine cavity.").
[160] 1996 Norplant Label.
[161] 2014 Mirena Label.
[162] 1996 Norplant label.
[163] 2014 Mirena Label.
[164] 2013 Skyla Label.
[165] November 16, 1992 letter from Victoria to Sobel (response to FOIA #2015-8544).

proposed labeling for Norplant to address spontaneous reports of Idiopathic intracranial hypertension which had been received for users of the Norplant System."[166]

Although useful as a hypothesis-generating tool, spontaneous adverse event reports suffer from numerous deficiencies and are the lowest form of evidence. As discussed above, reporting spontaneous adverse events is voluntary, and anyone can report an adverse event. There is often no medical verification of the reported facts, which may not accurately capture the event. The reports often lack necessary information about possible confounders, and incidence rates cannot be calculated. For these reasons, adverse event reports cannot be used to prove a causal association.[167]

Although FDA permitted Wyeth to list IIH as a Precaution in 1994 followed by an Adverse Reaction in 1995 and a Contraindication in 1996, evidence supporting the label language is minimal. By the time the Physician Labeling Rule was proposed in December 2000,[168] however, FDA had become more active in preventing potential over-warning. Over-warning poses two risks. First, unduly long labels may not be read or appreciated by physicians and/or patients. Therefore, adding warnings that lack scientific basis may cause those warnings that are grounded in science to lose their significance. Second, other patients and/or healthcare providers may be deterred from using necessary medications when faced with lengthy lists of warnings and precautions that may have no basis for causality. Here, for example, a warning about IIH that is not grounded in science could deter Mirena use by obese women, the very population for whom Mirena is specifically recommended and the population with the highest background risk for IIH.

Indeed, FDA's active role in preventing over-warning in labels is evident from the labeling negotiations surrounding Mirena. Aside from the labels for other IUDs, Bayer also relied on the Corporate Core Text (CCT) for Mirena in drafting its proposed label.[169,170] The version of the Mirena CCT in effect at the time that the proposed Mirena label was drafted contained a warning about venous thromboembolism (VTE), stating that recent epidemiologic studies of progestin-only pills had indicated that there may be a slightly increased risk of VTE, but that those results were not statistically significant.[171] In order to conform to the CCT,[172] the proposed Mirena label submitted to FDA included a nearly identical warning.[173] In its preliminary labeling comments, FDA struck that warning, which is evidence that FDA believed that it was not scientifically justified.[174] The lack of scientific justification has been confirmed through hindsight. A recent publication pooled the results of eight observational studies and found that neither progestin-only

[166] Record of November 10, 1992 Rarick conversation and November 16, 1992 letter from Victoria to Sobel (response to FOIA #2015-8544).
[167] openFDA, *About*, FDA.gov (updated 3/10/16).
[168] *Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels*, 65 Fed. Reg. 81082 (Dec. 22, 2000).
[169] MIR_JR_00185928.
[170] MIR_JR_00186596.
[171] MIR_CCDS_00000742.
[172] MIR_JR_00095903.
[173] MIR_INDNDA_00044480.
[174] MIR_INDNDA_00010880.

oral contraceptives nor Mirena increases the risk of VTE.[175] Since obese women are at a higher risk for VTE, inclusion of a VTE warning in the Mirena label absent scientific evidence to support such a warning could have discouraged Mirena use by the population for which it "may represent a particularly sound choice."[176]

Norplant ceased being marketed before passage of the PLR, which raised the evidentiary standard for adding a warning to a label. It is my opinion that the available evidence does not support an association (let alone a causal association) between IIH and Norplant.

4. The Medical Literature Does Not Provide Reasonable Evidence of an Association Between Norplant and IIH

Apart from spontaneous reports, there have been several publications regarding Norplant and IIH. These publications do not provide reasonable evidence of an association.

In 1993, Sunku reported that two patients developed IIH after implantation of Norplant.[177] The authors provided no information about whether the patients were obese or had experienced recent weight gain, two known risk factors for IIH. Symptoms arose well after implantation of Norplant (9 and 12 months), despite the fact that the release of LNG from Norplant (and, consequently, the serum blood concentrations of LNG) decreases over time. The authors concluded that the "possible" association between LNG implants and IIH could merely be "coincidental." This publication provides no reasonable evidence of an association between IIH and Norplant.

The 1995 publication by Wysowski and Green,[178] which evaluated 39 case reports of IIH among Norplant users, is no different. The fact that every patient for whom information about weight and body habitus was provided was overweight or obese points toward the strong association between excess weight and IIH and argues against a causal role for Norplant. Nor was there any clear temporal association between Norplant use and IIH symptomatology. Four patients experienced resolution of their symptoms while continuing Norplant use, and six had continuing symptoms after Norplant removal. Although sixteen patients had Norplant removed with resolution of symptoms, the diagnostic lumbar puncture is often therapeutic,[179] and IIH symptoms may also resolve spontaneously. Additionally, IIH patients are commonly treated with acetazolamide to reduce CSF pressure and encouraged to lose weight, both of which can be therapeutic.[180,181] At least some of the case reports indicated treatment with lumbar punctures

[175] Mantha S et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ. 2012; 345:e4944.
[176] MIR_INDNDA_00010880.
[177] Sunku AJ et al. Benign intracranial hypertension associated with levonorgestrel implants. Annals Neurol. 1993; 34:299.
[178] Wysowski DK & Green L. Serious Adverse Events in Norplant Users Reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. Obstet Gynecol. 1995; 85(4):538-542.
[179] Biousse V et al. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2012; 83(5):488-494.
[180] *Id.*
[181] NORDIC et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014; 311(16):23-30.

and/or acetazolamide. Ultimately, the authors concluded that the reporting rate (5.5 per 100,000 woman-years) did not exceed the expected rates of the disease, and that it was not possible to determine whether Norplant, obesity, and/or weight gain was related to the occurrence of IIH.

Moreover, a subsequent letter to the editor from Irving Sivin of the Population Council pointed out that Wysowski and Green had underestimated the years of experience of American women with Norplant and thereby overestimated the reporting rate by 34-50%.[182] Using a corrected measure of Norplant exposure, Sivin calculated a reporting rate of 2.8-3.7 per 100,000 woman-years, well within the background rate for women of childbearing age, and well below the rate expected for obese and overweight women of childbearing age. Sivin further noted that "continuation rates above 80 per 100 have been reported frequently by Norplant users, indicating that the experience base may be larger than estimates based on 80% continuation." Thus, according to Sivin, "the incidence of serious adverse events during Norplant use does not raise the 'suspicion of a causal association with Norplant.'" Nor, in my opinion, does the low reporting rate provide reasonable evidence of an association between IIH and Norplant.

Dr. Ross does not address the Sivin correction. He also claims that the original calculation of 5.5 per 100,000 is about 3 times higher than that observed in overweight women of childbearing age after adjusting for underreporting. Dr. Ross comes to this conclusion by employing what he terms the "widely accepted estimate that at most 10% of drug-associated adverse events are reported." This assumption ignores evidence that the extent of underreporting varies widely by medication, even within medications of the same class, based upon factors such as the publicity received and the incidence of the adverse event in the general population.[183] Without evidence regarding the extent of underreporting, it is inappropriate to assume that only 10% of adverse events are reported. Indeed, one of the sources upon which Dr. Ross relies expressly states that "[i]t would be inappropriate to apply a standard 'correction factor' based on the results of this study, since there is inevitably considerable variation in under-reporting for different drugs and types of ADRs, in different populations and at different points in time."[184] Moreover, that study found that the *median* reporting rate for serious adverse events such as IIH was 15%, 50% greater than the maximum reporting rate according to Dr. Ross.

Review of the 1995 letter to the editor by Alder further leads to the conclusion that there is no reasonable evidence of an association between Norplant and IIH.[185] The authors reported two cases of IIH after insertion of Norplant. While Dr. Ross asserts that Norplant was removed in both patients, the authors provide no such information. Even assuming that Norplant was removed, one patient had three IIH recurrences that required medication to control. If Norplant was the cause of the patient's IIH, one would not expect recurrences after removal. Alder also conducted a separate search of spontaneous adverse event reports and found 56 cases of "intracranial hypertension or disk edema," not specifically IIH. The authors provided no

[182] Sivin I. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. Obstet Gynecol. 1995; 86(2):318-320..
[183] McAdams M et al. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. Pharmacoepidemiology and Drug Saf. 2008; 17(3):229-39.
[184] Hazell L and Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006; 29(5):389-396.
[185] Alder JB et al. Levonorgestrel implants and intracranial hypertension. N Engl J Med. 1995; 332(25):1720-1721.

information about how many of these patients had excess weight or recent weight gain. And the authors concluded that "[l]evonorgestrel may have contributed to the onset of intracranial hypertension, or it may have had nothing to do with it."

In response to the Alder letter to the editor, Wyeth reviewed its own reporting databases.[186] Obesity was present in over three-quarters of reports of IIH in which information about weight was available, consistent with the well-known strong association between obesity and IIH. In more than half of cases for which information on follow-up was available, IIH did not resolve after Norplant was removed, further suggesting that Norplant was not the cause of the patients' IIH. Wyeth assumed a "highly conservative" annual discontinuation rate of 20% and calculated an observed reporting rate for IIH of 4.1/100,000 patient-years, nearly five times less than the expected rate for obese women. Because the reporting rate was in line with the incidence rate among the population seeking contraceptives (i.e., reproductive-age women), and because the vast majority of cases for which information was available occurred in the population with the highest risk for IIH (i.e., obese reproductive-age women), Alder provides no evidence of an association between Norplant and IIH.

In short, given the differences between Mirena and Norplant, and given lack of robust evidence supporting the IIH warning in Norplant, I conclude that Bayer's decision not to import Norplant's IIH language into the Mirena label was appropriate.

C. Because Early Mirena Data Provided No Support for Any Hypothesized Relationship Between IIH and Mirena, the Mirena Label Was Adequate at All Times Between 2000 and 2006.

As non-compelling as the evidence was for a relationship between Norplant and IIH when IIH was added to the Norplant label, the evidence was even less compelling with respect to any relationship between IIH and Mirena around the time of Mirena's launch. As noted above, no cases of IIH were reported during clinical trials of Mirena prior to the time of FDA approval.

Dr. Ross suggests that the August 2000 Mirena PSUR itself provided reasonable evidence of an association between Mirena and IIH. The PSUR includes a single case of a Mirena user with a history of IIH that pre-dates her Mirena usage, who experienced worsened headache *after Mirena was removed* and while receiving acetazolamide.[187] The patient had a "past medical history of acetazolamide toxicity."[188] There is no indication that the patient's IIH reoccurred as a result of her Mirena use, as Dr. Ross suggests. Indeed, the case report does not list any symptoms during the period in which Mirena had been inserted or indicate why Mirena was removed.

In any event, this PSUR was submitted before FDA's issuance of preliminary labeling comments in November 2000, and thus would have been available for FDA review before approval of the Mirena label.[189] If FDA had believed that this single case report constituted reasonable evidence

[186] Weber ME. Levonorgestrel implants and intracranial hypertension. N Engl J Med. 1995; 332(25):1721.
[187] MIR_INDNDA_00032125, at 32610.
[188] *Id.*
[189] MIR_INDNDA_00010880.

of an association between IIH and Mirena, it could have required a warning in the label prior to approval. FDA took no such action.

That was a reasonable decision, as this is not a situation where a single report can create a signal. Although FDA's 2005 *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Guidance* ("*FDA Guidance*") states that a single well-documented case report can create a signal "particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use,"[190] this case report is not such a case. The case report lacks important information, such as whether the patient had excess weight or recent weight gain, and is therefore not well-documented. It does not describe a positive rechallenge, and IIH is not "extremely rare" in the absence of Mirena use, particularly in the population of reproductive-age women to whom Mirena is preferentially prescribed (i.e., those who are obese). Furthermore, even if this single case with pre-existing IIH could result in a signal, a signal merely represents a concern about a potential safety issue that needs to be further evaluated, not an issue that must be immediately addressed in labeling.[191]

Dr. Ross also relies on the November 2001 PSUR[192] that reported three additional cases of IIH in Mirena users. By that time, there had been over two million users of Mirena, with only four reports of possible IIH. The reporting rate was therefore far below the incidence of IIH in the relevant population, even accepting Dr. Ross's assumption of massive underreporting. Given this finding, it was reasonable for Bayer not to engage in further investigation or labeling changes. Additionally, FDA received the PSUR and could have required additional investigation or a labeling change if it believed that approach to be correct.

D. Because There Is No Reasonable Evidence of a Causal Association Between Mirena and IIH, the Mirena Label Remained Adequate at All Times Since 2006

Since FDA's issuance of the PLR in 2006, a medication label must warn of an adverse event for which there is "reasonable evidence of a causal association."[193] In assessing whether there exists evidence of a causal relationship, the *FDA Guidance* calls for consideration of the following factors:

1. Occurrence of the adverse event in the expected time;

2. Absence of symptoms related to the event prior to exposure;

3. Evidence of positive dechallenge (whether the adverse event resolves or improves if the medication is stopped) or positive rechallenge (whether the adverse event returns when the drug is restarted);

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[190] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM250783.pdf.
[191] *Id.*
[192] MIR_AC_00174527.
[193] 21 C.F.R. §§ 201.57(c)(6), 314.70(c)(6)(iii)(A).

4. Consistency of the event with the established pharmacological/toxicological effects of the product;

5. Consistency of the event with the known effects of other products in the class;

6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and

7. Absence of alternative explanations (i.e., confounders) for the event.[194]

Good pharmacovigilance practices are described in FDA regulations and the *FDA Guidance*. One component of postmarketing safety surveillance is the collection, maintenance, reporting, and evaluation of spontaneous postmarketing adverse events. Although it is important to collect and analyze this data, as it may provide a signal indicating areas for further investigation, adverse event reports cannot be used to assess causality. FDA's own website even explains that "[s]ubmission of a safety report does not constitute an admission that [a] . . . product caused or contributed to the event."[195]

Based on my review of the materials in this case, Bayer met or exceeded its regulatory obligations in its periodic reporting to FDA. Periodic reports were submitted in a timely fashion. Those reports summarized all necessary adverse event reports, included extensive information about serious adverse events when possible, and contained periodic analyses of specific adverse events. Bayer also submitted expedited reports as required for all cases of serious and unexpected adverse events, both foreign and domestic.

Bayer has regularly and repeatedly evaluated the cases of IIH it receives, and a discussion of IIH cases is included in the PSURs. Three times since 2008, Bayer has also conducted signal analyses of IIH adverse event reports, in an effort to determine whether additional study of IIH was warranted. These signal analyses, which were conducted in 2008, 2014, and 2015, are discussed below.

1. 2008 Signal Assessment

Dr. Juliane Schoendorf, of Bayer's Global Pharmacovigilance, conducted a comprehensive signal assessment regarding IIH and Mirena in 2008, at the request of the British health authority, MHRA.[196] Bayer included its findings in its 2008 PSUR. The estimated post-marketing experience from launch until the end of 2007 was close to 33.06 million women-years. The total number of insertions estimated from the number of units sold was over 12.76 million. Bayer located no articles referring to IIH with Mirena, and found no confirmed cases of IIH in

[194] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM250783.pdf.
[195] openFDA, *About*, FDA.gov (updated 3/10/16) ("Submission of a safety report does not constitute an admission that medical . . . product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.").
[196] MIR_AC-R_00178489-00178493.

clinical trials. A search of the company's ADR database for cases of benign intracranial hypertension, intracranial pressure increased, and papilledema located 24 cases of diagnosed or suspected IIH.

The calculated reporting frequency was 0.07 cases per 100,000 woman-years of exposure.[197] Of cases that provided information on body weight, 80% were overweight or obese, suggesting that excess weight, a known risk factor for IIH, may have contributed to the development of IIH. There was not a common duration of onset, and some cases reported onset of symptoms even prior to Mirena insertion. In 3 out of 8 cases for which follow-up information was available, symptoms did not resolve upon discontinuation of Mirena. There was no unambiguous case of positive dechallenge, as patients whose symptoms resolved generally underwent lumbar puncture for diagnosis and received other treatment in addition to removal of Mirena.

Given that Mirena is specifically recommended for the population most at risk for IIH (overweight or obese females of childbearing age), it is expected that some Mirena users will experience IIH. The finding of 0.07 cases per 100,000 woman-years is extremely low, such that even assuming that only 10% of cases were reported (as Dr. Ross hypothesizes), the "corrected" rate would be 0.7 cases per 100,000 woman-years, one-fifth the incidence rate among women of child-bearing age (3.5 per 100,000 woman-years) and less than one-twenty fifth the incidence rate among obese women of child-bearing age (19.3 per 100,000 woman-years). Given this reporting rate, the large presence of confounders, the lack of a consistent temporal relationship, and the absence of a single unambiguous case of positive dechallenge, the data did not indicate that Mirena use would increase the risk for developing IIH. Indeed, MHRA agreed with Bayer that there was "insufficient evidence of an association between Mirena and BIH."[198] It was therefore reasonable for Bayer not to conduct observational studies or add an IIH warning to the Mirena label.

2. 2014 Signal Assessment

In 2014, Bayer identified an increase in IIH adverse event reporting as a result of legal claims against the company, and as a result, it conducted another signal assessment.[199] Bayer reviewed the epidemiology and its adverse events database, as well as the scientific literature from the past 10 years. It found that evidence from larger epidemiological studies for an association of Mirena with IIH was still lacking.

Bayer did report on three IIH cases identified in the post-approval Mirena clinical trials. One clinical study report described a 37-year-old obese woman (BMI 31) who had her first Mirena replaced after 5 years of use, and who developed IIH 10 months after receiving her second Mirena (total use: 5 years, 10 months). No further action was taken, and the patient recovered

[197] Bayer assumed a 10% annual discontinuation rate. This assumption is reasonable, given that recent studies have reported discontinuation rates of 11%-12% after one year. Moreau C. Frequency of discontinuation of contraceptive use: results from a French population-based cohort. Hum Reprod. 2009; 24(6):1387-1392; Peipert JF. Continuation and Satisfaction of Reversible Contraception. Obstet. Gynecol. 2011; 117(5):1105-1113.
[198] MIR_JSEU_00780138.
[199] MIR_PKEU_00699321-00699335.

without removing Mirena.[200,201] Given these facts, Bayer appropriately agreed with the investigator that IIH was not related to Mirena. Another clinical study patient who received a different LNG-based IUD (Skyla/Jaydess), had pre-existing IIH, and "during the study no worsening of the pseudotumor occurred."[202] In a third case, a patient developed diplopia shortly after insertion. It was unclear whether she met the criteria for IIH, given that a lumbar puncture was never performed, but symptoms resolved without removal of Mirena.[203] Given these facts, Bayer correctly determined that the patient's symptoms were not related to her Mirena usage.

Bayer also conducted a search for all IIH cases in its adverse events database up to March 31, 2014. There were 66 reports consistent with IIH, and the cumulative postmarketing experience was approximately 99.4 million woman-years, giving a reporting rate of 0.07 per 100,000 women-years. In other words, the reporting rate remained unchanged from 2008, despite a surge in legal cases reported in 2014. Eight cases were reported from lawyers, 7 in the 4 months prior to the report, and the information reported about these cases was minimal. Again, even crediting the unsubstantiated level of under-reporting hypothesized by Dr. Ross, the findings of this signal analysis suggest no increased risk of IIH among Mirena patients.

Moreover, Bayer's analysis of the event reports again revealed information inconsistent with a causal relationship. First, in 81% of cases for which information was available, a known risk factor for IIH — excess weight or recent weight gain — was present.[204] Second, information on the time interval between insertion of Mirena and diagnosis or exacerbation of IIH revealed no conclusive pattern. Onset occurred in almost equal numbers with 2 months of use, between 2 months and 6 months, between 6 months and a year, and between 1 year and 2 years.[205] In nearly one-third of cases, onset of symptoms occurred between 2 years and 11 years, a fact that itself suggests the absence of a causal relationship between Mirena and IIH, particularly given the decreased LNG dose released by Mirena over time.[206] Third, not only was there no definitive case of positive dechallenge, but some patients saw no improvement in symptoms after removal of Mirena, while others recovered without Mirena removal. Even among those who saw improvement after having Mirena removed and undergoing treatment, improvement sometimes occurred years after removal.

3. 2015 Signal Assessment

Bayer conducted yet another signal assessment in 2015[207] in response to a new publication by Etminan[208] suggesting a slight increase in IIH risk with the use of Mirena based on a search of the FAERS database. Bayer's review of the Etminan publication noted that there are many limitations to the use of FAERS data, and that the authors used incorrect and overinclusive

[200] MIR_BSR_36776.
[201] MIR_ISEU_268963.
[202] MIR-JSEU_01446069.
[203] MIR-JSEU_01057343.
[204] MIR_PKEU_00699331.
[205] MIR_PKEU_00699331-00699332.
[206] *Id.*
[207] MIR_KCOPLEY_JSEU_00000046-00000067.
[208] Etminan M et al. Risk of intracranial hypertension with intrauterine levonorgestrel. Ther Adv Drug Saf. 2015; 6(3):110-113.

search terms, reported no effort to limit the database search to women of reproductive age, and provided no information about the number of women who had excess weight or had experienced recent weight gain.[209] I have reviewed the Etminan publication myself and share Bayer's concerns. Most troubling, when Bayer attempted to reproduce the data presented, Bayer was unable to reproduce Etminan's disproportionality scores.[210] Instead, Bayer's search of the FAERS and WHO databases revealed no over-proportional reporting of IIH for Mirena users compared to all other cases in female patients aged 17-45.[211]

In light of the foregoing, the Etminan publication does not provide reasonable evidence of a causal association between Mirena and IIH. This conclusion is further supported by the results of the authors' separate retrospective cohort study, which found no statistically significant difference in the risk of IIH between users of Mirena and users of two combined oral contraceptives.[212] Numerous studies have found no statistically significant relationship between the use of oral contraceptives and IIH.[213,214,215,216,217]

Bayer's 2015 signal assessment also analyzed an abstract by Raju Rai,[218] which reported an increased risk of IIH among Mirena users in a small case control study. Bayer noted that the small percentage of Mirena users who agreed to participate in telephone interviews could have led to substantial selection bias, that the interview questions presented concerns about recall bias, that the authors used different methodologies to collect cases and controls, that the authors reported no attempt to verify the accuracy of the coded diagnoses, and that the authors appeared not to have controlled for confounders such as excess weight and recent weight gain.[219] In light of these limitations, the Rai abstract, which has not been peer reviewed or published, does not provide reasonable evidence of a causal association between Mirena and IIH. The abstract authors even acknowledge that the publication does not establish a causative role for Mirena, that its conclusions are preliminary, and that removal of Mirena in a typical IIH patient is not warranted.[220]

Bayer's 2015 signal assessment identified 114 cases of IIH reported with Mirena and one with Jaydess (Skyla), with postmarketing exposure of 120 million woman-years, giving an estimate of 0.09 cases per 100,000 women-years. It was noted that stimulated reporting in the context of US

[209] MIR_KCOPLEY_JSEU_00000047-00000048.
[210] MIR_KCOPLEY_JSEU_00000049-00000056.
[211] *Id.*
[212] Etminan M et al. Risk of intracranial hypertension with intrauterine levonorgestrel. Ther Adv Drug Saf. 2015; 6(3):110-113.
[213] Digre KB. Pseudotumor cerebri and pregnancy. Neurology. 1984; 34(6):721-729
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[216] Giuseffi V et al. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. Neurology. 1991; 41(2):239-244.
[217] Radhakrishnan K. Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci. 1993; 116(1):18-28.
[218] Rai R et al. Idiopathic intracranial hypertension and papilledema. ARVO 2015 Annual Meeting Abstract.
[219] MIR_KCOPLEY_JSEU_00000062-00000063.
[220] Rai R et al. Idiopathic intracranial hypertension and papilledema. ARVO 2015 Annual Meeting Abstract.

lawsuits had artificially increased the reporting rates of IIH. The cases included 46 reports in the context of litigation and 32 reports submitted by lawyers. Again, however, this reporting rate is lower than that found among women of childbearing age, even accounting for significant underreporting. As before, Bayer's analysis revealed that the vast majority of women were overweight or obese or had experienced recent weight gain, that there was no consistent duration between Mirena insertion and time of IIH onset, and that there was no unambiguous case of positive dechallenge.

4. Dr. Ross's Criticisms of Bayer's Pharmacovigilance Are Unfounded

Dr. Ross offers several criticisms of Bayer's signal assessments, all of which are unfounded.

First, Dr. Ross claims that Bayer's Standard Operating Procedure for signal detection failed to require Bayer to submit signal analyses to FDA, with signals that were not validated simply being discarded without provision for further follow-up. Regardless of the terms of Bayer's internal procedural manual, Bayer submitted each of its signal assessments as part of its PSURs.[221,222]

After receiving safety information such as that contained in Bayer's signal assessments, "FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class)."[223] In other words, pursuant to the *FDA Guidance*, upon receipt of Bayer's signal assessments, FDA would have reviewed the information provided and information about other contraceptives (possibly including Norplant), and made its own assessment. The FDA never asked Bayer to add a warning about IIH.

Bayer's decision not to conduct observational studies also followed the *FDA Guidance*, which provides that when no signal is detected, there is no need to take additional steps apart from continued monitoring of future adverse event reports. The *FDA Guidance* makes clear that "risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps."[224] It further recommends that "sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. . . . *Signals warranting additional investigation* can be further evaluated through carefully designed non-randomized observational studies of the product's use in the 'real world' and randomized trials."[225] None of the three signal reviews conducted by

[221] MIR_INDNDA_00246210.
[222] MIR_INDNDA_00340337.
[223] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM250783.pdf.
[224] *Id.*
[225] *Id.*

Bayer triggered any need for additional investigation. Bayer's continued monitoring of adverse event reports fully comports with its pharmacovigilance obligations.

Second, Dr. Ross alleges that by focusing "primarily on the potential alternative explanation of obesity as the cause for these cases," Bayer's analysis "was directed at excluding a relationship between Mirena and IIH, rather than an objective exploration of the data." He concludes that Bayer failed to "address whether the risk of weight gain in Mirena users . . . could lead to obesity and thereby raise the risk of IIH." But the *FDA Guidance* recommends that "[i]n assessing case reports, . . . sponsors [should] look for features that may suggest a causal relationship between the use of a product and the adverse events."[226] Bayer's signal assessments were focused on features that may suggest a causal relationship, or lack thereof, between the use of Mirena and IIH (e.g., duration of onset, dechallenge information, and the presence of alternative explanations). Moreover, contrary to Dr. Ross's assertion, there is no evidence suggesting that Mirena causes significant or rapid weight gain.[227] Regardless, the IIH reporting rate among Mirena patients remains low for women of childbearing age, and especially for overweight or obese women.

Third, Dr. Ross further suggests that Bayer should have compared reporting rates or numbers of adverse events reported between Mirena and ParaGard or other IUDs on the market. I disagree. The *FDA Guidance* states that a comparison of two or more reporting rates should be viewed with "extreme caution."[228]

Dr. Ross reports that he searched the FAERS database for cases of IIH in users of Mirena, Skyla, Liletta, and ParaGard, finding 22, 1, 0, and 0 reports of IIH, respectively. His analysis is highly misleading. Although the FAERS does contain 22 case reports of IIH among Mirena users, multiple reports were submitted for several patients, and the database contains reports for just 14 unique patients. The information provided in many reports is incomplete, as is common in adverse event reports, but the information listed is nonetheless consistent with the results of Bayer's signal assessments and the broader academic literature. For example, of the six patients for whom weight was reported, mean weight was 218 pounds (median weight 195 pounds). For the seven patients whose reports included insertion and removal dates, time with Mirena ranged from 5 days to 1096 days, with no discernible pattern of onset (mean and median duration of onset of 412 days and 205 days, respectively).

Dr. Ross's claim that there are no IIH reports among ParaGard users is similarly misleading, as there are only 2,266 total adverse event reports for ParaGard in the openFDA database, compared to 73,330 for Mirena. This disparity in event reporting may reflect that ParaGard use is far less common than Mirena use, or may alternatively be explained by the many factors that influence reporting rates. Regardless of why there is such a large disparity between the total number of adverse event reports for ParaGard as compared to Mirena, the disparity highlights

[226] *Id.*
[227] Vickory Z et al. Weight change at 12 months in users of three progestin-only contraceptive methods. Contraception. 2013; 88(4):503-08.
[228] *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, U.S. Department of Health and Human Services, Food and Drug Administration (Mar. 2005), http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM250783.pdf.

FDA's warning to view such comparisons with "extreme caution." Even if the number of adverse event reports were comparable between the two IUDs, ParaGard, unlike Mirena, is not specifically recommended for obese women, so one would expect to see fewer reports of IIH among ParaGard users.

Dr. Ross's search results for Liletta and Skyla are also not informative. Because Liletta was first marketed in the US in April 2015, and because Dr. Ross searched FAERS data only through September 2015, one would not expect to see many reports of IIH among Liletta users. Similarly, Skyla gained FDA approval in January 2013, over a decade after Mirena. Indeed, a search of the openFDA database revealed no adverse events associated with Liletta and only 1,430 adverse events associated with Skyla.[229]

Finally, Dr. Ross alleges that Bayer applied "a nonexistent regulatory standard" by concluding in its signal reports that "confirmed evidence for a causal association of levonorgestrel implant use and intracranial hypertension is lacking." Dr. Ross ignores Bayer's statement that "the available data for Mirena do currently not indicate that Mirena use would be associated with an increased risk for developing IIH." In other words, Bayer concluded that there was no evidence, confirmed or otherwise, of an association between Mirena and IIH, let alone of a causal association.

E. Other LNG Contraceptives

While Dr. Ross relies heavily on the Norplant label to suggest that Mirena should include an IIH warning, it is worth noting that other marketed LNG- and progestin-containing contraceptives do not carry such a warning. First, Nexplanon, a single capsule implant containing the progestin etonogestrel was approved in 2006 and has no IIH warning.[230,231] Second, although many marketed oral contraceptives contain LNG, none of them warn about IIH.[232] Third, FDA has approved two additional LNG-releasing IUDs since Mirena: Skyla in 2013, and Liletta in 2015. By the time of their approvals, FDA had seen Mirena signal assessments for IIH, but FDA and did not require an IIH warning for Skyla or Liletta.[233,234]

Dr. Ross notes that Jadelle is an approved LNG-containing implant, although it has never been marketed in the US. Like its predecessor Norplant, Jadelle is a subcutaneous implant that delivers systemic distribution of LNG. Mirena, on the other hand, has a different mechanism of action, providing contraceptive effect primarily through local effects within the uterus. Although the Jadelle label contains an IIH warning and contraindication for those with a history of IIH, such language is identical to the Norplant label. Jadelle is the successor product of Norplant, and it contains an IIH warning only for historic reasons.[235] The fact that Jadelle contains an IIH warning does not justify its inclusion in the Mirena label.

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[229] I queried the openFDA database using researchAE.com.
[230] 2006 Nexplanon Label; 2015 Nexplanon Label.
[231] 2015 Nexplanon Label.
[232] DailyMed search, https://dailymed nlm nih.gov/dailymed.
[233] 2013 Skyla Label.
[234] 2015 Liletta Label.
[235] Nov. 13–14, 2015 Dep. Tr. of Juliane Schoendorf, at 44:14–44:20, 79:6–79:10, 114:8–114:11, 148:11–148:15, 170:11–170:14.

VII. Opinions

1. It is my opinion that Bayer and its predecessors met or exceeded their regulatory responsibilities in the development of Mirena. They submitted adequate evidence of Mirena's safety and effectiveness to FDA to support approval of Mirena for five years of continuous use for pregnancy prevention and for the treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.

2. In my opinion, Bayer followed FDA regulations for the Mirena labeling, including in its label all risks of Mirena for which there was reasonable evidence of an association.

3. In my opinion, Bayer appropriately collected and analyzed reports of adverse events and all available safety data from its clinical studies, postmarketing surveillance, and published literature, and reported that information to FDA in a timely manner.

4. In my opinion, Mirena is an important product for women's health with a favorable risk/benefit profile. The labeled risks of the product are far outweighed by its superior effectiveness in preventing unintended pregnancy and the serious health risks that are associated with pregnancy and delivery or termination.

5. In my opinion, there has never been a confirmed safety signal related to idiopathic intracranial hypertension in Mirena users. While a small number of IIH reports have been submitted to Bayer and FDA, the reporting rate is well below the expected rate of IIH in similar patients in the general population, even accounting for underreporting. Moreover, factors suggestive of a causal association are lacking.

6. In my opinion, the Mirena label has always been adequate with respect to IIH. At no time before 2006 was there reasonable evidence of an association between Mirena and IIH. At no time since 2006 has there been reasonable evidence of a causal association between Mirena and IIH.

Basis for Opinions

My opinions set forth in this report are expressed to a reasonable degree of medical and scientific certainty. I reserve the right to supplement these opinions if additional information becomes available, and I reserve the right to respond to the testimony of others. In forming my opinions, I relied upon my knowledge of the FDA regulations, policies and procedures, as well as my own training and clinical experience as an obstetrician/gynecologist providing women's health care, my experience at FDA as a medical officer generally, and my experience with following the regulations in making decisions regarding product approval, labeling modifications, and other regulatory matters for a wide range of drug products.

Dena R. Hixon M.D.

Dena R. Hixon, M.D.

APPENDIX A

CURRICULUM VITAE

Dena R. Hixon, M.D.

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Dena R. Hixon is the sole member of Pharmaceutical Lifecycle Consulting LLC. She offers consulting services in the field of drug development and regulation, including clinical and regulatory considerations for both new and generic drugs, from early development through product approval and postmarket surveillance.

Dr. Hixon has 13 years of regulatory experience with the US Food and Drug Administration (FDA), serving as a primary reviewer and team leader in the Division of Reproductive and Urologic Drug Products before becoming the Associate Director for Medical Affairs in the Office of Generic Drugs.

During her service in the Office of New Drugs, Dr. Hixon was responsible for reviews of Investigational New Drug (IND) submissions, protocol proposals for various phase 1 and 2 studies and Special Protocol Assessments for phase 3 studies, New Drug Applications (NDAs), labeling, and postmarketing safety reports. She also conducted and/or participated in numerous meetings with industry sponsors, including pre-IND meetings, end-of-phase 2 meetings, pre-NDA meetings, and other guidance meetings. As a medical officer, she conducted primary reviews of clinical data and clinical study proposals for evaluating safety and efficacy. As a team leader, she trained other medical officers and reviewed their work. She also summarized the reviews of all relevant disciplines and made recommendations on approval of applications.

Dr. Hixon reviewed a wide variety of drugs for reproductive and urologic indications, including the following:

- Contraception, including oral, injectable, vaginal, and transdermal hormonal contraceptives, other vaginal contraceptives, and intrauterine devices
- Emergency contraception
- Premenstrual syndrome
- Polycystic ovarian syndrome
- Hormone replacement
- Female sexual dysfunction
- Erectile dysfunction

As Associate Director for Medical Affairs in the Office of Generic Drugs, Dr. Hixon served as an advisor to the office regarding safety issues and other clinical considerations for generic drugs. She supervised a team of medical officers and pharmacists reviewing clinical endpoint bioequivalence studies for locally acting products, and developing recommendations for establishing bioequivalence of complex generic products to their respective reference products. She reviewed many locally-acting products, transdermal products, and other products for which pharmacokinetic studies alone may not be adequate to establish bioequivalence. This work involved reviewing and understanding various aspects of the development and regulation of new drug products across all offices and divisions of the Office of New Drugs.

Dr. Hixon's work in the Center for Drug Evaluation and Research (CDER) included participation in a number of inter-office committees and working groups, including the following:

- She served on the Pregnancy Labeling Task Force from 1999 to 2005, participating in the development of the 2008 Proposed Rule on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling.
- She served on the FDA Drug Safety Oversight Board from its inception in 2005 until 2008, considering various emerging safety issues and FDA regulatory actions and public communications.
- She served on the CDER Pediatric Review Committee from 2002 until 2010, evaluating Written Requests to conduct studies of drugs for pediatric patients to qualify for pediatric exclusivity.
- She served on the CDER Pediatric Exclusivity Board from 2002 until 2011, considering study reports submitted in response to Pediatric Written Requests to determine whether pediatric exclusivity should be granted.
- She served on the Follow-On Protein Pharmaceutical Planning Committee in 2004-2005 for planning and executing two public workshops on the topic of Follow-On Protein Pharmaceuticals.
- She served on a working group to establish the Unapproved Drugs Compliance Policy Guide in 2006, evaluating risks of an unapproved product.

Dr. Hixon served as an instructor for CDER reviewers at the following internal conferences:

- She presented The Roles of the Medical Officer in the Drug Review Process for New Reviewers Workshop on numerous occasions from 1999 to 2006.

- She presented Clinical Considerations in Generic Drug Development to the Office of Generic Drugs and to CDER training conferences on numerous occasions from 2003 to 2010.
- She participated in CDER Scientific Rounds on numerous occasions from 2006 to 2010 as a presenter and/or panelist.
- She presented generic drug findings to the Drug Safety Oversight Board in 2007.

She also gave presentations at external conferences on various regulatory considerations including the following:

- Generics Yes video presentation in 2003 to promote public acceptance of generic drugs
- Annual Generic Pharmaceutical Association Fall Technical Conferences 2003 to 2011, presenting various clinical considerations in generic drug development and review
- FDA public workshop on follow-on protein pharmaceuticals in 2005, serving as a moderator for the Office of Generic Drugs.
- FDA and Generics Drugs—An Interactive Forum, University of Rhode Island College of Pharmacy, 2008: presenting Clinical Considerations for Generic Drugs
- CDER Forum for International Drug Regulatory Authorities, 2005 and 2006, presenting the CDER review process.

Publications

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Education and Work History

College

Bridgewater College, Bridgewater, VA 1972-1976
Degree: B.A. Biology 1976
Honors: Summa cum laude

Medical School

University of Maryland School of Medicine, Baltimore, MD 1976-1980
Degree: M.D. 1980

Residency Training

- Family Practice—Harrisburg Hospital, Harrisburg, PA 1980-1983
  Board Certified in Family Practice, 1983
- Obstetrics and Gynecology—Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA 1983-1986
  Board Certified in Obstetrics and Gynecology 1989

Medical Practice

- Central Connecticut Obstetricians and Gynecologists, P.C., Bristol, CT, 1986-1989
- Chesapeake Obstetrics, Easton, MD 1989-1998

Hospital Affiliation

Bristol Hospital, Bristol, CT 1986-1989
Memorial Hospital at Easton, Easton, MD 1989-1998
Chairman, Department of OB/GYN 1992-1994
Credentials and Bylaws Committee 1992-1997
Executive Committee 1991-1995
Infection Control Committee 1991-1997

Locum Tenens

CompHealth, Salt Lake City, UT, assignments as follow:
Dr. Rebecca Green, Nashua NH, 1991
Antietam Health Services, Inc., Hagerstown, MD, 1992
Kauai Medical Group, OB/GYN, Lihue, HI 1992

U.S. Food and Drug Administration 1999-2011

Center for Drug Development and Research
Division of Reproductive and Urologic Drug Products
Medical Officer January 19, 1999 to July 14, 2002
Medical Officer Team Leader November 19, 2000 to July 14, 2002

Office of Generic Drugs
Associate Director for Medical Affairs July 14, 2002 to August 1, 2011
Acting Director, Division of Clinical Review August 1 to November 5, 2011

APPENDIX B

Dena Hixon, M.D.
Materials Reviewed

Academic Literature

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